

REMARKS***Regarding the Substitute Sequence Listing and Related Amendments***

The Substitute Sequence Listing submitted herewith corrects some obvious errors in the original Sequence Listing submitted for parent application USSN 09/603,713 on June 27, 2000 and includes additional sequences present in the original specification as filed and omitted from the original sequence listing which are required to conform to 37 C.F.R. §§1.821 to 1.825. SEQ ID NOS:32-34 have been added to the Substitute Sequence Listing from Figure 1, and SEQ ID NOS:36-39 have been added from Table 1, in order to include those amino acid sequences of 4 or more residues.

The amended paragraphs on page 7, page 8 (Figure 8 description), page 33 (Table 1), page 36, page 47, and page 49 have been amended to be consistent with the sequence listing, as described in greater detail below. Similarly, the deletion of the previous sequence listing from the specification has been requested. Claim 24, as presented in the Examiner's Amendment, has also been amended to include the "SEQ ID NO:" for OM99-2, consistent with the Substitute Sequence Listing, and as described in greater detail below.

Table 1 has been amended to include sequence identifiers for SEQ ID NOS:36-39 (Site #1-4) and retention of the original notations for the amino acid positions in SEQ ID NO:3 in parentetical form. Also amended were the formats for other sequence identifiers present in the table. In addition, the sequence identifiers have been aligned with the table rows showing the amino acid sequences for SEQ ID NOS:22-26 and a "Comments" header has been added for clarity. This also required repositioning the notations "C[^] is cysteic acid" and "Three sites cleaved in a peptide: VGSGLLSRK (SEQ ID NO:30)" under the "Comments" header. A clean copy of the amended Table 1 is also enclosed for the convenience of the Examiner.

The "Organism" numeric identifier <213> describing the Genus and species or "Artificial Sequence" and/or numeric identifier <223> "Description of Artificial Sequence" data elements have been changed in some cases (i.e., SEQ ID NOS:4-29) to properly reflect their presentation as free text in the Specification.

SEQ ID NO:8 appears in the Specification on page 14, line 25, as "Asp-Thr/Ser-Gly-", where the original Sequence Listing had entered this sequence as a tetrapeptide. One of ordinary skill in the art would recognize that the aspartic protease cleavage motif consists of a tripeptide where the second amino acid residue can be either Thr or Ser. The Substitute Sequence Listing submitted herewith entered this sequence with the second residue represented as "Xaa" with a Feature describing the alternative residues at that position.

SEQ ID NOS:27, 29 and 35 have included a Feature to describe the modified amino acids at those positions containing a non-peptide bond in the form of the transition-state isostere hydroxyethylene. SEQ ID NO:35, the OM99-2 inhibitor, was added to the Substitute Sequence Listing to reflect the modified form of the sequence presented on page 36, line 20, and Figures 3B and 8 as opposed to the unmodified form in SEQ ID NO:28 on page 6, lines 15-16, and page 47, line 8. SEQ ID NO:28 has been retained in the form containing no modified amino acids or non-peptide bonds to distinguish this sequence from the modified form containing the transition-state isostere.

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a Statement Pursuant to 37 CFR § 1.821(f), and a paper copy of the sequence information that is identical to the computer readable copy and paper copy of the Substitute Sequence Listing filed in the related patent application 10/773,754, in accordance with 37 C.F.R. §1.821(c) and (e). The Statement Pursuant to 37 CFR §1.821(f) includes a request to transfer the computer readable form which was mailed on June 14, 2004, (and received by the US PTO on June 17, 2004) in related patent application USSN 10/773,754 to the present patent application as the computer readable form for the instant application.

As noted in the accompanying Statement Pursuant to 37 CFR §1.821(f), related patent application USSN 10/773,754 is a continuation of USSN 09/845,226, filed April 30, 2001, which is a divisional of **USSN 09/603,713**. The present application is a continuation of **USSN 09/603,713**. Both USSN 10/773,754 and the present application claim priority to USSN 60/141,363; 60/168,060;

60/177,836; 60/179,368 and 60/210,292. Based on the claimed subject matter, the inventors of the present application are Jordon J.N. TANG and Arun K. GHOSH.

It is believed that these amendments do not represent new matter.

Regarding the Brief Descriptions of the Drawings and the Drawings

Pursuant to a telephone discussion with the Examiner on March 23, 2007 regarding clarification of the objections to the "Color Photographs and Color Drawings" set forth in the Examiner's Amendment at page 4, the Applicants have amended the Brief Descriptions of the Drawings for Figures 6, 7 and 9 (all appearing on page 8 of the specification), to be consistent with the black and white drawings submitted with the application as filed. The same amendments to the drawings were previously entered in related case U.S. 10/773,754.

It is believed that these amendments do not represent new matter.

Also pursuant to discussion with the Examiner on March 23, 2007, the Applicants confirm that Figure 5(A-E) were submitted as a photocopy of a black and white photograph depicting crystals and thus do not require entry via a petition, as they were not color photographs, consistent with 37 C.F.R. §1.84(b1). A replacement photocopy of Figure 5(A-E) with improved photocopy quality is provided herewith.

The Applicants respectfully request entry of the above-described amendments and entry of the Substitute Sequence Listing as described above and in the accompanying Statement Pursuant to 37 CFR §1.821(f).

CONCLUSION

Applicants respectfully request entry of this amendment. If it is determined that a telephone conference would expedite the entry of this amendment or that additional information is needed, the Examiner is earnestly encouraged to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 578352001702. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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Table 1: Substrate Specificity of Memapsin 2

Site #	Substrate	P4	P3	P2	P1	P1'	P2'	P3'	P4'	Comments
1	Pro-memapsin 2	R	G	S	M	A	G	V	L	SEQ ID NO:36 (aa 12-18 of SEQ ID NO:3)
2		G	T	Q	H	G	I	R	L	SEQ ID NO:37 (aa 23-30 of SEQ ID NO:3)
3		S	S	N	F	A	V	G	A	SEQ ID NO:38 (aa 98-105 of SEQ ID NO:3)
4		G	L	A	Y	A	E	I	A	SEQ ID NO:39 (aa 183-190 of SEQ ID NO:3)
5	Oxidized insulin B-chain'	H	L	C^	G	S	H	L	V	SEQ ID NO:22
6		C^	G	E	R	G	F	F	Y	SEQ ID NO:23 C^ is cysteic acid
7	Synthetic peptide				V	G	S	G	V	SEQ ID NO:24 SEQ ID NO:25
8			V	G	S	G	V	L	L	SEQ ID NO:26
9		G	V	L	L	S	R	K		Three sites cleaved in a peptide: VGSGVLLSRK (SEQ ID NO:30)
10	Peptide	L	V	N	M	A	E	G	D	SEQ ID NO:9